937,723

PATENT SPECIFICATION

NO DRAWINGS

937,723

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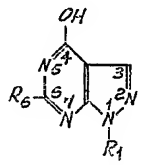
COMPLETE SPECIFICATION

Pyrazolo-Pyrimidines and process for their manufacture

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new pyrazolo-pyrimidines, a process for their manufacture and pharmaceutical preparations containing them.

The present invention provides pyrazolo-[3,4-d]pyrimidines of the formula

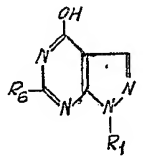


and tautomers thereof, and physiologically tolerable salts of these compounds. In the above formula R_1 represents an alkyl, cycloalkyl or cycloalkylalkyl group. Examples of such substituents are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl-(1), pentyl-(2), pentyl-(3), 2-methyl-butyl-(3) or hexyl, cyclopentyl or cyclohexyl, or cyclopentyl- or cyclohexyl-methyl, -ethyl or -propyl groups.

R_6 represents an alkyl group, for example a lower alkyl group, for example one of those mentioned above in connection with R_1, with the proviso that when R_6 and R_1 are alkyl groups and R_6 contains fewer than 3 carbon atoms, R_1 represents an alkyl group containing more than two carbon atoms.

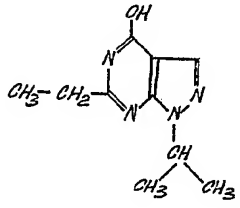
The new compounds possess valuable pharmacological properties. Above all they have a coronary dilating action. They also have an inhibiting action on the central nervous system. Accordingly, the new compounds are useful as medicaments, more especially for treating circulatory disturbances of the myocardium, and they are also useful as intermediate products for the manufacture of such medicaments. With respect to the use as coronary dilatating agents, the aforesaid 1,6-dialkyl compounds are superior to compounds in which each of the two alkyl groups in positions 1 and 6 contains less than 3 carbon atoms.

Especially valuable as coronary dilatators are compounds of the formula



and tautomers and salts thereof, in which formula R_1 represents a lower alkyl group, for example, methyl, ethyl, propyl, isopropyl, butyl-(2), 3-methyl-butyl-(2), pentyl-(2), pentyl-(3), or a cycloalkyl group, for example, cyclopentyl or cyclohexyl, and R_6 an alkyl group, with the proviso that in a 1:6-dialkyl-compound one of the alkyl groups R_1 and R_6 contains more than two carbon atoms.

There may be mentioned especially the 1-isopropyl - 4 - hydroxy - 6 - ethyl - pyrazolo[3:4 - d]pyrimidine of the formula



and physiologically tolerable salts thereof.

Substituents contained in the resulting

compounds can be converted one into another within the afore-mentioned groups; thus, a nitrophenyl group can be reduced in a known manner to form an aminophenyl group or a phenyl group may be nitrated.

The invention also provides a process for the manufacture of the above new compounds, wherein a 2 - R_1 - 3 - amino - pyrazole - 4-carboxylic acid ester is reacted with a nitrile of the formula R_6—CN, in which R_1 and R_6 have the meanings given above.

The condensation of the aminopyrazole to form the pyrazolo-pyrimidine is preferably carried out at a raised temperature, if desired, in the presence of a diluent and/or condensing agent under atmospheric or superatmospheric pressure. Surprisingly, it has been observed that it is very advantageous to carry out the reaction with the use of a 2-R_1-3-amino-pyrazole-4-carboxylic acid ester, for example, an alkyl ester thereof, and of a nitrile of the formula R_6CN, using a condensing agent, preferably an alkali metal, for example sodium, if desired, in the form of its amide, hydride or an alcoholate, or another strong base such as trimethylbenzyl-ammonium hydroxide and using a diluent, such as benzene, toluene, xylene or an ether.

The resulting hydroxy compounds can be converted in the usual manner into their salts with bases such, for example, as their metal salts, such as alkali metal salts, for example sodium or potassium salts, for example by treatment with a suitable base. The salts in their turn can be converted into the free hydroxy compounds, advantageously by treatment with acids.

The new pharmacologically valuable compounds and their salts can be used, for example, in the form of pharmaceutical preparations containing the said compounds in admixture or conjunction with an organic or inorganic pharmaceutical excipient suitable for enteral or parenteral administration. Suitable excipients are substances that do not react with the compounds described, such, for example, as gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, water, benzyl alcohols, gums, polyalkylene glycols, cholesterol or other known medicinal excipients. The pharmaceutical preparations may be, for example, tablets or dragees, or in liquid form solutions, suspensions or emulsions. They may be sterilised and/or may contain assistants such as preserving, stabilising, wetting or emulsifying agents. They may further contain other therapeutically useful substances. The preparations are formulated by conventional methods. They contain, for example, 5 to 50 mg, preferably 10 mg, of the active substance per dosage unit and about 1—70%, preferably 5—50%, of active substance.

The final products of the present process are also valuable intermediates, for example for the manufacture of the 4-mercapto compounds described in our Application No. 17107/61 (Serial No. 937,726). It is, for example, possible to replace the hydroxyl group in position 4 of the 1-R_1-6-R_6-pyrazolo-[3:4-d]pyrimidines by halogen atoms, such as chlorine or bromine, for example by treatment with a phosphoric acid halide, such as phosphorus oxychloride or phosphorus pentachloride, or to convert it into a free mercapto group in the usual manner, for example by treatment with phosphorus pentasulphide. The halogen atom in a resulting 4-halogen compound can be exchanged, for example, by treatment with thiourea, a metal salt of hydrogen sulphide or a mercaptan.

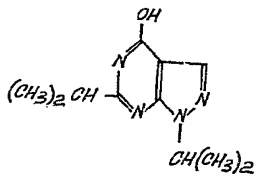
Insofar as the starting materials used in the present process are new, they can be prepared by known methods.

Starting materials preferably used in the present process are those which give rise to the final products designated above as being particularly valuable. The starting materials may also be used in the form of their salts.

The following Examples illustrate the invention.

EXAMPLE 1

39.6 grams of 2-isopropyl-3-amino-4-carbethoxypyrazole and 9.2 grams of finely distributed sodium are introduced into 160 cc of isobutyronitrile. During the course of 1 hour the mixture is heated to 110° C., stirred for 4 hours at this temperature, and then allowed to cool. 15 cc of ethanol are added, the whole is evaporated to dryness under vacuum, and the residue is taken up in 100 cc of 2N-sodium hydroxide solution, and the alkaline solution is extracted by being shaken with chloroform. The aqueous phase is adjusted to pH 5—6 with 5N-hydrochloric acid, whereupon a solid product precipitates which is repeatedly recrystallised from ethanol, to yield 1-isopropyl-4 - hydroxy - 6 - isopropyl - pyrazolo[3:4-d]pyrimidine of the formula

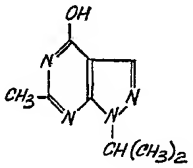


in white crystals melting at 175—177° C.

EXAMPLE 2

2.3 grams of sodium are added while cooling with ice to a solution of 9.9 grams of 2-isopropyl - 3 - amino - 4 - carbethoxypyrazole in 50 cc of acetonitrile. The temperature must not be allowed to rise above 30° C. during the reaction. On completion of the exothermic

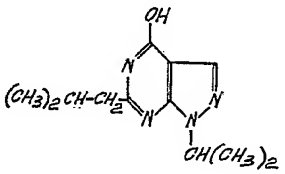
reaction, the mixture is heated for 4 hours at 90 to 95° C., then allowed to cool, treated with 100 cc of ethanol and evaporated to dryness under vacuum. The residue is treated with 150 cc of 2N-sodium hydroxide solution, and the excess acetonitrile is extracted with chloroform. The aqueous phase is adjusted to pH 3—4 with 5N-hydrochloric acid; after prolonged standing, a solid precipitate forms which is filtered off and recrystallised from ethanol, to yield 1 - isopropyl - 4 - hydroxy-6 - methylpyrazolo[3:4 - d]pyrimidine of the formula



in white crystals melting at 195—196° C.

EXAMPLE 3

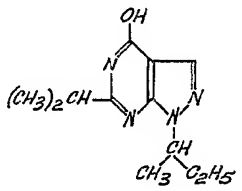
19.8 grams of 2-isopropyl-3-amino-4-carbethoxypyrazole and 4.6 grams of finely distributed sodium are introduced into 100 cc of isovaleronitrile. During the course of 1 hour the mixture is cautiously heated to 110° C., maintained for 4 hours at this temperature, allowed to cool, treated with 150 cc of ethanol and evaporated to dryness in vacuum. The residue is taken up in 150 cc of 2N-sodium hydroxide solution, the alkaline solution is extracted with chloroform to remove the undissolved matter and then adjusted to pH 4—5 with 6N-hydrochloric acid, whereupon a solid precipitate forms which is recrystallised from ethanol, to yield 1-isopropyl - 4 - hydroxy - 6 - (2^1 - methyl-propyl) - pyrazolo[3:4 - d]pyrimidine of the formula



in white crystals melting at 114—116° C.

EXAMPLE 4

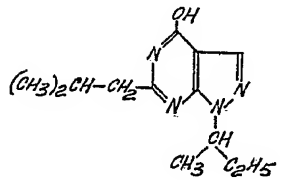
9.2 grams of sodium and then 42.2 grams of 2 - secondary butyl - 3 - amino - 4-carbethoxypyrazole are added to 130 cc of isobutyronitrile. During the course of about 30 minutes the mixture is heated to 110—120° C., stirred for 5 hours at this temperature and then allowed to cool, treated with absolute ethanol and evaporated in vacuum. The residue is treated with dilute sodium hydroxide solution and extracted with chloroform. The alkaline aqueous solution is treated with active carbon and filtered. The clear filtrate is adjusted to pH 6, whereupon 1-secondary butyl-4-hydroxy - 6 - isopropyl - pyrazole[3:4-d]pyrimidine of the formula



separates out. After recrystallisation from ether + petroleum ether, it melts at 146—148° C.

EXAMPLE 5

9.2 grams of sodium and then 42.2 grams of 2-secondary butyl - 3 - amino - 4 - carbethoxypyrazole are added to 130 cc of isovaleronitrile. The mixture is slowly heated to 110—120° C., stirred for 5 hours at this temperature and then allowed to cool, treated with absolute ethanol and evaporated in vacuum. The residue is treated with dilute sodium hydroxide solution and extracted with chloroform. The alkaline aqueous solution is treated with active carbon and filtered. The clear filtrate is adjusted to pH 6 with 5N-hydrochloric acid, and the residue is recrystallised from ether + petroleum ether, to yield 1 - secondary butyl - 4 - hydroxy - 6 - (2^1-methyl - propyl) - pyrazolo[3:4 - d]pyrimidine of the formula

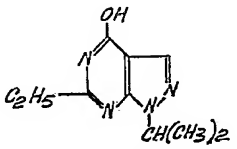


melting at 115—116° C.

EXAMPLE 6

2.3 grams of finely distributed sodium are introduced while cooling with water into a solution of 9.9 grams of 2-isopropyl-3-amino-4-carbethoxypyrazole in 100 grams of propionitrile. On completion of the exothermic reaction, the mixture is stirred while being heated for 4 hours at 100—110° C., allowed to cool, then treated with 100 cc of alcohol and evaporated to dryness under vacuum. The residue is taken up in 150 cc of 2N-sodium hydroxide solution; the alkaline solution is

freed from undissolved matter by extraction with chloroform and then adjusted to pH 6 with 6N-hydrochloric acid, whereupon a smeary product separates out which is recrystallized from alcohol, to yield 1-isopropyl-4 - hydroxy - 6 - ethyl - pyrazolo[3:4-d]pyrimidine of the formula



in colourless crystals melting at 180 to 182° C.

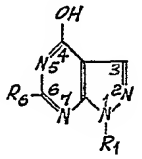
EXAMPLE 7

1 - isopropyl - 4 - hydroxy - 6 - ethyl-pyrazolo[3:4 - d]pyrimidine is made up in the usual manner into tablets of the following composition:

1 - isopropyl - 4 - hydroxy - 6-ethyl - pyrazolo[3:4 - d]pyrimidine	10
lactose	35
non-swelling starch	20
wheat starch	10
silicon dioxide	10
arrowroot	12
magnesium stearate	0.5
talcum	6

WHAT WE CLAIM IS:—

1. A pyrazolo[3,4 - d]pyrimidine of the general formula

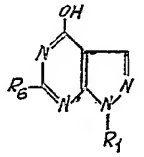


or a tautomer thereof, in which formula R_1 represents an alkyl, cycloalkyl or cycloalkyl-alkyl group and R_6 represents an alkyl group, with the proviso that when R_6 and R_1 represent alkyl groups and R_6 contains less than 3 carbon atoms, R_1 represents an alkyl group containing more than 2 carbon atoms.

2. A physiologically tolerable salt of a compound as claimed in claim 1.

3. An alkali metal salt of a compound as claimed in claim 1.

4. A compound of the formula



or a tautomer thereof, in which R_1 represents a lower alkyl group or a cycloalkyl group, and R_6 represents an alkyl group, with the proviso that in a 1:6-dialkyl compound one of the alkyl groups R_1 and R_6 contains more than 2 carbon atoms.

5. A physiologically tolerable salt of a compound as claimed in claim 4.

6. An alkali metal salt of a compound as claimed in claim 4.

7. 1 - Isopropyl - 4 - hydroxy - 6 - ethyl-pyrazolo[3,4 - d]pyrimidine

8. 1 - Isopropyl - 4 - hydroxy - 6 - methyl-pyrazolo[3,4 - d]pyrimidine.

9. 1 - Isopropyl - 4 - hydroxy - 6 - (2^1-methyl - propyl) - pyrazolo[3:4 - d]pyrimidine.

10. 1:6 - Di - isopropyl - 4 - hydroxy-pyrazolo[3:4 - d]pyrimidine.

11. 1 - Secondary - butyl - 4 - hydroxy-6 - isopropyl - pyrazolo[3:4 - d] - pyrimidine.

12. 1 - Secondary - butyl - 4 - hydroxy-6 - (2^1 - methyl - propyl) - pyrazolo[3:4-d]pyrimidine.

13. A physiologically tolerable salt of the compound claimed in any one of claims 7 to 12.

14. An alkali metal salt of the compound claimed in any one of claims 7 to 12.

15. A new compound as claimed in claim 1 and described in any one of Examples 1 to 6 herein.

16. A process for the manufacture of a pyrazolo[3,4-d]pyrimidine as claimed in claim 1, or a physiologically tolerable salt thereof, wherein a 2-R_1-3-amino-pyrazole-4-carboxylic acid ester is reacted with a nitrile of the formula R_6—CN, in which starting materials R_1 and R_6 have the meanings given in claim 1.

17. A process for the manufacture of a compound as claimed in claim 1 conducted substantially as described in any one of Examples 1—6 herein.

18. A pharmaceutical preparation which comprises a compound as claimed in claim 1 or 4 in admixture or conjunction with a pharmaceutically suitable carrier.

19. A pharmaceutical preparation which comprises a salt as claimed in any one of claims 2, 3, 5 and 6 in admixture or conjunction with a pharmaceutically suitable carrier.

20. A pharmaceutical preparation which comprises the compound claimed in any one of claims 7 to 12 in admixture or conjunction with a pharmaceutically suitable carrier.

21. A pharmaceutical preparation which comprises a salt as claimed in claim 13 in admixture or conjunction with a pharmacuetically suitable carrier.

22. A pharmaceutical preparation which comprises a salt as claimed in claim 14 in

admixture or conjunction with a pharmaceutically suitable carrier.

23. A tablet having substantially the composition given in Example 7 herein.

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